REMARKS

Finalization of Restriction Requirement

In response to the finalization of the restriction requirement in the 8 November 2001 Office Action, applicants have amended claims 2, 10 and 16 have been amended herein to reflect the elected subject matter. It therefore is requested that the withdrawal of claim 2 be rescinded in favor of retention of claim 2 as amended herein, and that the objection to claims 5 (dependent, *inter alia*, under claims 2 and 10), 10 and 16 be withdrawn in respect of claims 2, 5, 10, and 16, as amended and now pending in the application.

Replacement of Title and Abstract

The Title and Abstract have been amended herein to set forth the term "carcinogenic," as requested by the Examiner.

Replacement of the Specification

The Examiner objected to the framing of the originally filed specification. In response, applicants have rewritten the specification to comply with the Examiner's suggested format.

Amendment/Addition of Claims

New claims 17 and 18 have been added, coextensive with the Examiner's statement at page 13 (paragraph 12) of the November 8, 2002 Office Action that the subject matter now embodied in the new claims is "free of the art of record." Consistent therewith, it is requested that the patentability of claims 17 and 18 be responsively confirmed by the Examiner.

New claims 19 and 20 have been added, to claim further aspects of the invention consistent with the description at page 3, lines 1-4.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

In response to the rejection of claims 3-6 and 10-16 on §112, second paragraph grounds, the claims have been amended to obviate the issues raised by the Examiner.

Claim 3 has been amended to recite "the inhibition of the poly(ADP ribose) polymerase has been effected by a transgenic operation," thereby obviating the issue raised by the Examiner concerning correspondingly worded claim 14. Further, claim 3 has been amended to recite the depended-from claims 2 and 10 in ascending order as alternative dependencies, thereby avoiding the potential confusion speculated by the Examiner in paragraph 10 of the November 8, 2002 Office Action.

Claims 4, 5 and 6 have likewise been amended to recite depended-from claims in ascending order, to avoid the potential confusion speculated by the Examiner in paragraph 10 of the November 8, 2002 Office Action.

Claim 5 has been amended to recite "carcinogenic agents" for consistency with the amended specification and claims.

Claim 10 also has been amended for consistency of use of the term "carcinogenic."

Claims 10 and 16, rejected as omitting "essential steps," have been correspondingly amended to incorporate the recital proposed by the Examiner.

Claims 10 and 11 have also been amended to omit the recital of the definite article ("the") in reference to "poly(ADP ribose) polymerase" in such claims, thereby obviating the antecedent basis issue raised by the Examiner at page 12 of the November 8, 2002 Office Action.

Claim 11 has been further amended herein to make clear that the recited DNA repair disturbance is "caused by a transgene of the transgenic mammal inhibiting poly(ADP ribose) polymerase," thereby obviating the transgenic characterization issue raised by the Examiner.

Claim 14 has been amended to recite that "the inhibition of the poly(ADP ribose) polymerase has been effected by a transgenic operation," thereby obviating the transgenicity issue cited by the Examiner at page 13 of the Office Action.

In response to the §112, first paragraph issue raised by the Examiner in respect of the recital in claim 16 of "transgenic mammals" in line 5 ("as to whether there are more than one transgenic mammal"), the Examiner's attention is directed to the fact that the recital at issue, *viz.*,

> "wherein **said mammal** is selected from the group consisting of **transgenic mammals** having a genome wherein the expression of poly (ADP ribose) polymerase is altered by an inserted gene encoding a dominant negative poly(ADP ribose) polymerase" (emphasis added)

has no infirmity, since the Markush selection group in fact encompasses a multiplicity of transgenic mammals that share the characteristic of being transgenically altered in the recited manner, namely, by "an inserted gene encoding a dominant negative poly(ADP ribose) polymerase" and ONE such mammal is utilized from the selection group (the previously recited "a mammal").

Based on the foregoing, the now-pending claims 2-6 and 10-20 fully comply with the requirements of 35 U.S.C. §112, second paragraph.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 3-6 and 10-16 in the November 8, 2002 Office Action on §112, first paragraph grounds, as lacking written description evidencing possession of the invention as to a representative number of species of the claimed invention, and as lacking reasonable "enablement for any and all transgenic mammals and other claimed embodiments encompassed by the claimed invention."

These grounds of rejection are traversed, and the Examiner is requested to reconsider, and on reconsideration, to withdraw same, based on the following remarks.

The making of transgenic animals must be acknowledged as involving standard procedures that are in current and continuous use in thousands of laboratories worldwide.

Since living animals are involved, there will always be a certain variability, so that a success cannot be guaranteed for every experiment that is performed - for example, in the case of a transgene that has been previously identified and successfully demonstrated, and for which it has been shown that the desired expression was obtained for several, independently generated founder animals, it cannot be taken for granted that a successful expression will be obtained for each and every founder animal, newly produced,

BUT it is fundamental knowledge and well-established procedure in the fields of genetics and molecular biology that the producti n of recombinant or mutated animals is followed by screening, which allows the selection of successfully altered organisms to be achieved.

Further, within the existing knowledge and skill of the art, the successful generation of founder animals for a given transgene, enables application of the same transgene to different animals.

The applicants have already shown (through their previous work) that transgenic animal lines showing successful expression can be generated with an acceptable effort. The inventive mammals of the present invention are readily generated, on the basis of the written description in the instant application, using art-recognized standard procedures within the skill of the art, *viz.*, by the steps of:

1. microinjecting fertilized egg cells (according to published methods), using the plasmid DNA described in the instant application;
2. implanting the resulting eggs into "nanny mothers" and testing the resulting newborn animal for the presence of the transgene (according to published methods), to identify a founder animal; and
3. testing several of the founder animals for the correct expression of the transgene with "immuno methods" using specific antibodies.

In the applicants' experience, a success rate of about 30% is achieved, this being a good value in the field of transgenesis experiments and justifying the designation "standard procedure."

The invention is therefore fully enabled.[2]

Further, given the ready applicability of the applicants' teachings to a variety of mammalian species, of which murine species are but one illustrative example, the fact that diverse mammalian species will

[2] The fact that some experimentation is necessary does not preclude enablement; all that is required is that the amount of experimentation "must not be unduly extensive." *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 224 USPQ 409, 413 (Fed. Cir. 1984). Even a considerable amount of time and effort is permissible for such experimentation, if the procedures involved are routine in light of the applicant's disclosure. "[A] considerable amount of experimentation is permissible if it is merely routine." *Ex parte Jackson*, 217 USPQ 804, 807 (1982). See also *PPG Industries, Inc. v. Guardian Indus. Corp.*, 75 F.3d at 1564, 37 USPQ2d at 1618, 1623 (Fed. Cir 1996), where the court stated that even where some experimentation is necessary to reduce an invention to practice, the enablement requirement is satisfied where: (1) the experimentation is routine; or (2) the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention.

behave more or less alike, and within a range, permits the skilled artisan, within the skill of the art, to readily apply the teachings of the present application to such diverse mammalian species.

There is no written description or enablement infirmity in the present application. The written description requirements entail sufficient disclosure of the invention to evidence possession of the claimed invention at the time of filing.[3] The present application satisfies such criterion.

Enablement of a claimed invention requires that one of skill in the field of the invention be able to practice the invention based on the disclosure of the patent application without undue experimentation. This applicants have done.

Applicants' invention relates to a transgenic mammal and an *in vivo* method for the identification of carcinogenic agents that relies on a defect in the DNA repair system of the test animal wherein the enzyme poly (ADP ribose) polymerase is inhibited. The applicants' teachings may be implemented on the basis of the disclosure in the instant application, with standard and routine techniques known to those of ordinary skill in the art of genetic manipulation, and are applicable within the skill of the art to create test animals of various types, without undue experimentation.

The Examiner therefore is requested to reconsider, and on reconsideration to withdraw, the rejection of claims 3-6 and 10-16 on §112, first paragraph grounds.

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[3] See Regents of the *Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991); *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993); and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991). It is not necessary for applicants' specification to read like a clinical protocol in order to show that the Applicants were in possession of the claimed inventions. See also *Northern Telecom, Inc. v. Datapoint Corp.*, 15 U.S.P.Q.2d 1321, 1329 (Fed. Cir. 1990) ("[T]he patent document is not intended to be a production specification."). The law is well settled on the point of providing sufficient disclosure to one skilled in the art. Specifically, the court stated in *In re Alton*, 37 USPQ 2d, 1578 (Fed. Cir. 1996) that "if a person of ordinary skill in the art would have understood the inventor to have been in his possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." Further, as stated by the court in *In re Eickmeyer*, 202 USPQ 655 (C.C.P.A., 1979) "[t]o satisfy the description requirement of section 112 (First Paragraph), an application must contain sufficient disclosure expressly or inherently, to make it clear to one skilled in the art that the applicant was in possession of the subject matter." *Ipsissimis verbis* disclosure is not necessary to satisfy the written requirement of section 112.

Fee Payable for Added Claims

The addition of claims 17-20 herein increases the total number of independent claims from 3 to 7. Accordingly, the added claims fee of $168 is payable, and such amount, together with the amount of $55 for the one-month extension of time requested in the following section, for a total fee of $223, is hereby authorized to be charged to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

Request under 37 CFR 1.136 for One Month Extension of Time

Request hereby is made under the provisions of 37 CFR 1.136 for a one month extension of the term for reply to the November 8, 2001 Office Action, extending the term from February 8, 2002 to March 8, 2002. The fee of $55 for such extension of time, together with the added claims fee of $168 (see preceding section), for a total fee of $223, is hereby authorized to be charged to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

CONCLUSION

Claims 2-6 and 10-20 as amended/added herein, are in form and condition for allowance. Favorable action is requested.

If any issues remain outstanding, the Examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss their resolution, so that this application may be passed to issue at an early date.

Respectfully submitted,

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